(FILE 'HOME' ENTERED AT 11:20:12 ON 09 APR 2001)

FILE 'PCTFULL' ENTERED AT 11:20:18 ON 09 APR 2001
L1 1 S WO9941220/PN
L2 1 S WO9966924/PN
L3 0 S CAPLUS, USPATFUL

FILE 'CAPLUS, USPATFULL' ENTERED AT 11:32:02 ON 09 APR 2001
L4 224 S FIBROBLAST MIGRATION
L5 24657 S FIBRINOGEN
L6 17 S L4 AND L5
L7 86 S (FIBROBLAST MIGRATION)/AB
L8 18400 S FIBRINOGEN/AB
L9 3 S L7 AND L8

=> s (fibroblast migration)/clm

'CLM' IS NOT A VALID FIELD CODE
L10 2 (FIBROBLAST MIGRATION)/CLM

=> d 1-2 clm

L10 ANSWER 1 OF 2 USPATFULL
CLM What is claimed is:
1. A method of inhibiting scar tissue formation during the healing of wounds, comprising the steps of administering to a host suffering from tissue wounding a growth factor neutralizing antibody specific against a
growth factor selected from the group consisting of TGF-.beta..sub.1, TGF-.beta..sub.2 and PDGF, wherein the antibody neutralizes the stimulation of macrophage infiltration, **fibroblast migration**, extracellular matrix synthesis or deposition by fibroblasts, in the wound area before the granulation phase in a dosage effective to reduce activity of the growth factor.

2. A method according to claim 1, wherein the growth factor neutralizing
antibody is selected from the group consisting of anti-TGF-.beta..sub.1 antibody, anti-TGF-.beta..sub.2 antibody, and anti-PDGF-antibody.

3. A method of inhibiting scar tissue formation during the healing of wounds, comprising the steps of administering to a host suffering from tissue wounding a growth factor neutralizing antibody specific against a
growth factor selected from the group consisting of TGF-.beta..sub.1, TGF-.beta..sub.2 and PDGF, wherein the antibody neutralizes the stimulation of macrophage infiltration, **fibroblast migration**, extracellular matrix synthesis or deposition by fibroblasts, in the wound area during the granulation phase in a dosage effective to reduce activity of the growth factor.

4. A method according to claim 3, wherein the growth factor neutralizing
antibody is selected from the group consisting of anti-TGF-.beta..sub.1 antibody, anti-TGF-.beta..sub.2 antibody, and anti-PDGF-antibody.

5. A method according to claim 1, wherein the growth factor neutralizing antibody is encapsulated.

6. A method according to claim 5, wherein the capsule is degradable by an external stimulus to release the growth factor neutralizing antibody.

7. A method according to claim 6, wherein the external stimulus is selected from the group consisting of UV light, in vivo enzymes, ultrasound and heat.

8. A method according to claim 1, wherein the growth factor neutralizing antibody is bound to a binding molecule.

9. A method according to claim 8, further comprising the step of detaching the binding molecule from the growth factor neutralizing antibody.

10. A method according to claim 9 wherein the binding molecule is detached from the growth factor neutralizing antibody by an external stimulus selected from the group consisting of UV light, in vivo enzymes, ultrasound and heat.

11. A method according to claim 1, further comprising the step of administering the growth factor neutralizing antibody in a pharmaceutically acceptable carrier.

12. A method according to claim 11, wherein the pharmaceutically acceptable carrier is selected from the group consisting of a neutral sterile cream, gel, aerosol and powder for topical application.

13. A method according to claim 11, wherein the pharmaceutically acceptable carrier is selected from the group consisting of a sterile solution for injection, irrigation and inhalation.

14. A method according to claim 11, wherein the pharmaceutically acceptable carrier comprises a sterile dressing for topically covering a wound.

15. A method according to claim 11, wherein the pharmaceutically acceptable carrier is selected from the group consisting of a biopolymer and a polymer for implanting within the wound.

16. A method according to claim 1, further comprising the step of administering a fibroblast growth factor with the growth factor neutralizing antibody.

17. A method according to claim 3, wherein the growth factor neutralizing antibody is encapsulated.

18. A method according to claim 17, wherein the capsule is degradable by an external stimulus to release the growth factor neutralizing antibody.

19. A method according to claim 18, wherein the external stimulus is selected from the group consisting of UV light, in vivo enzymes, ultrasound and heat.

20. A method according to claim 3, wherein the growth factor neutralizing antibody is bound to a binding molecule.

21. A method according to claim 20, further comprising the step of detaching the binding molecule from the growth factor neutralizing antibody.

22. A method according to claim 21 wherein the binding molecule is detached from the growth factor neutralizing antibody by an external stimulus selected from the group consisting of UV light, in vivo enzymes, ultrasound and heat.

23. A method according to claim 3, further comprising the step of administering the growth factor neutralizing antibody in a pharmaceutically acceptable carrier.

24. A method according to claim 23, wherein the pharmaceutically acceptable carrier is selected from the group consisting of a neutral sterile cream, gel, aerosol and powder for topical application.

25. A method according to claim 23, wherein the pharmaceutically acceptable-carrier is selected from the group consisting of a sterile solution for injection, irrigation and inhalation.

26. A method according to claim 23, wherein the pharmaceutically acceptable carrier comprises a sterile dressing for topically covering a wound.

27. A method according to claim 23, wherein the pharmaceutically acceptable carrier is selected from the group consisting of a biopolymer and a polymer for implanting within the wound.

28. A method according to claim 3, further comprising the step of administering a fibroblast growth factor with the growth factor neutralizing antibody.

L10 ANSWER 2 OF 2 USPATFULL
CLM What is claimed is:

1. A method for promoting wound healing comprising topically applying to a wound an effective amount of a compound selected from the group consisting of synthetic polysulfated monosaccharides and oligosaccharides and their pharmaceutically acceptable salts in a pharmaceutically acceptable carrier.

2. The method of claim 1 wherein the oligosaccharide contains three or more sulfate groups.

3. The method of claim 1 wherein the compound is a disaccharide or monosaccharide.

4. The method of claim 1 wherein the oligosaccharide is persulfated.

5. The method of claim 3 wherein the disaccharide is sucrose.

6. The method of claim 1 wherein the polysulfated oligosaccharide is sucrose octasulfate.

7. The method of claim 1 or 6 wherein the salt is an alkali metal salt.

8. The method of claim 1 or 6 wherein the salt is a potassium or sodium salt.

9. The method of claim 1 wherein the oligosaccharide is applied in a liquid form.

10. The method of claim 9 wherein the liquid is water.

11. The method of claim 9 wherein the liquid is isotonic salt solution.

12. The method of claim 9 wherein the oligosaccharide is present at a concentration of 0.1 to 1.0 mg/ml.

13. The method of claim 9 wherein sucrose octasulfate is present at a concentration of 0.28 mg/ml.

14. The method of claim 1 wherein the oligosaccharide is applied in combination with collagen.

15. The method of claim 14 wherein the combination of collagen and oligosaccharide is applied as a liquid suspension.

16. The method of claim 15 wherein the suspension contains 2 to 15 mg/ml collagen.

17. The method of claim 16 wherein the suspension comprises 0.28 mg/ml sucrose octasulfate and 8.75 mg/ml collagen suspended in an isotonic salt solution.

18. The method of claim 1 wherein the oligosaccharide is encapsulated in a polymer or other carrier which is capable of effecting sustained release of the oligosaccharide.

19. The method of claim 1 wherein healing of skin or bone wounds is promoted.

20. The method of claim 1 wherein the compound is applied to a wound in a bone.

21. A method of promoting wound healing by means of neovascularization and **fibroblast migration** comprising topically applying to a wound an effective amount of a compound selected from the group consisting of synthetic polysulfated monosaccharides and oligosaccharides and their pharmaceutically acceptable salts in a pharmaceutically acceptable carrier.

L6 ANSWER 12 OF 17 USPATFULL

SUMM . . . of collagen implants as wound healing matrices. U.S. Pat. No. 4,453,939 discusses a wound healing composition of collagen with a **fibrinogen** component and a thrombin component, and optionally fibronectin. U.S. Pat. No. 4,970,298 discusses the usefulness of a biodegradable collagen matrix. . .

SUMM . . . simulates the fetal in utero wound healing matrix. U.S. Pat. No. 5,631,011 discloses a composition of HA and fibrin or **fibrinogen**.

SUMM . . . Raben (1996) studied platelet-derived growth factor (PDGF). Henke et al. (1996) disclosed that chondroitin sulfate proteoglycan mediated cell migration on **fibrinogen** and invasion into a fibrin matrix, while Nakamura et al. (1997) concluded that chondroitin sulfate did not affect wound closure. . . in a corneal epithelial wound. Henke et al. (1996) also disclosed that an anti-CD44 antibody blocked endothelial cell migration on **fibrinogen**. U.S. Pat. No. 5,641,483 discloses topical gel and cream formulations containing human plasma fibronectin for healing of cutaneous wounds. Schultz. .

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SUMM . . . 1992; Kishida et al. 1992). Schor et al. (1996) disclose that only the gelatin binding domain of FN (GBD) stimulates **fibroblast migration** into a 3-D matrix of native type I collagen fibrils at femtomolar concentrations; whereas peptides of the other FN functional domains do not stimulate **fibroblast migration** in this assay at femtomolar to nanomolar concentrations. Schor et al. (1996) also disclose that the RGDS-containing cell binding domain of FN does, however, stimulate **fibroblast migration** in the transmembrane (or "Boyden chamber") assay. Steed et al. (1995) disclose that the RGD peptide matrix (known as Argidene. . .

DETD **Fibroblast Migration** Assays: Transmigration from Organotypic Collagen Gel Constructs into Fibrin/Fibronectin Gels or Outmigration Over Protein coated surfaces

DETD . . . Clark 1997), dried fibrin fibril-coated dishes are washed once with PBS and fibroblast-contracted collagen gels are placed on the surface. **Fibrinogen**, at a final concentration of 300 .mu.g/ml, is mixed with DMEM and 1.0 U/ml thrombin, added to the wells so. . .

DETD Assay plates are prepared as described under **fibroblast migration** assays. The assay for measuring fibroblast adhesion to matrix proteins are performed essentially as described (Gailit et al. 1993) except. . .

DETD . . . fibroblast transmigration. To do this, FN was selectively removed from each matrix material. First, residual FN was removed from the **fibrinogen** preparation by affinity chromatography on gelatin. After removal of FN, fibroblast transmigration into the fibrin clot was decreased by about. . . be restored by the addition of FN to the fibrin gel. Optimal cell movement was observed with 30 .mu.g/ml, a FN:**fibrinogen** ratio of 1:10, the physiological plasma ratio. In FIG. 15A, migration induced by 30 ng/ml PDGF-BB (shaded bars; open bars: 0 35 ng/ml PDGF) was measured under the usual assay conditions. The **fibrinogen** preparation used to form the fibrin gel was untreated (left), treated with gelatin-Sepharose to remove FN (center), or treated with. . .

DETD . . . conditions. Contraction of the collagen gel was stimulated with serum as usual (FBS) or with 30 ng/ml PDGF-BB (PDGF). The

fibrinogen preparation used to form the fibrin gel was untreated (Fb), treated with gelatin-Sepharose to remove FN (Fb-FN), or treated with. . .

DETD Fibronectin (FN) is required for **fibroblast migration** through both fibrin clots and hyaluronic acid (HA) gels. Therefore, the FN domains necessary for migration were examined.

DETD . . . HV0 on these plates, which presented both the RGD cell-binding and heparin-binding domains, respectively, in a non contiguous array, enhanced **fibroblast migration** to approximately 45% of the maximum level seen with intact FN (FIG. 10A). When recombinant FN protein CHV0, which contains. . .

DETD To further define which Hep II and IIICS subdomains are involved in **fibroblast migration** on FN, synthetic peptides previously shown to be active in cell adhesion were manufactured from sequences in the 12th, 13th,. . .

DETD . . . peptides gave essentially the same results. In aggregate these data demonstrate that 3 major domains of FN are required for **fibroblast migration**.

DETD . . . 2.0 15 .+-. 3.7

.sup.a All proteins and peptides were assayed at concentrations from 3 to 400 nmol/l, however, maximum **fibroblast migration** was observed when 120 nmol/l protein was added to assay plates. Therefore, the data shown were acquired from plates coated with 120 nmol/l FN, recombinant peptides or FN120.

.sup.b **Fibroblast migration** on fibronectin (FN) was normalized to 100%.

.sup.c Data are presented as mean .+-. SD percent migration of that

L6 ANSWER 15 OF 17 USPATFULL

SUMM . . . pastes containing coagulation-enhancing factors. One such coagulation enhancing substance employed to assist a cessation of bleeding or "hemostasis" is human **fibrinogen**, most commonly employed as a "fibrin glue".

SUMM Fibrin glue is composed of a mixture of human **fibrinogen** and bovine thrombin. It is sold as a kit containing separate vials of **fibrinogen** and thrombin solutions. These solutions are mixed together and applied to the wound in various ways, including as a paste,. . .

SUMM . . . of such solution, further hemorrhage occurs and the solutions are washed away by intense bleeding. Despite the headway made in **fibrinogen** compositions and surgical techniques, these pitfalls in achieving hemostasis underscore the need for development of a suitable product.

SUMM . . . fibrin glue, marketed in Europe consists of a biodegradable collagen patch onto which is impregnated bovine thrombin, aprotinin and human **fibrinogen** (the "TAF" patch). An example of a TAF patch is the TachoComb.RTM. patch marketed in Europe by Hafslund Nycomed Pharma,. . .

SUMM A major drawback to the use of fibrin glue and the TAF patch is that both contain human **fibrinogen**, a protein purified from human blood. Because of the high risk of HIV and hepatitis viral contamination, the Food and Drug Administration revoked the use of human **fibrinogen** in the United States in 1978. In addition to the safety concerns, human **fibrinogen** purified from human plasma is very expensive.

SUMM . . . one hemostatic agent, epsilon aminocaproic acid. The patch does not require as an ingredient any exogenous human protein, such as **fibrinogen**, which thereby avoids introduction of unsafe contaminating viruses. The present hemostatic patch is inexpensive, easy to use, thermally stable, and. . .

DETD . . . been discovered that EACA functions as a hemostatic agent in a patch in a manner that approximates the effectiveness of **fibrinogen**, a coagulation factor that, in solution, converts to fibrin in the presence of thrombin. **Fibrinogen** is an active ingredient found in other hemostatic patches. EACA, however, is devoid of the hazards that accompany use of **fibrinogen**.

DETD Another advantage of EACA is that it contains no foreign peptides of animal origin. For example, a non-human **fibrinogen** hemostatic agent in some humans will trigger an immune response or allergic-like reaction.

DETD . . . "E." This embodiment, "GE", preferably also can contain calcium, "G(Ca++)E." Advantageously, the GE or G(Ca++)E patch need not contain or **fibrinogen** to function effectively to control hemorrhage of a parenahymal organ. As a result, both GE and G(Ca++)E, have good thermal. . . a lengthy period, even in absence of refrigeration. Both also are much less expensive to make than patches which contain **fibrinogen**.

DETD . . . = collagen or collagen (Helistat .RTM.), respectively

E = EACA

(Ca++) = calcium

T = thrombin

R = RGD peptide

P = protamine sulfate

F = **Fibrinogen**
(f) = freshly applied compound (Example 7)
GT (Ca++) E
= "Hemarrest .TM." patch

DETD . . . enzyme substrate interactions. In particular, the gelatin foam structure enhances contact between thrombin provided exogenously in the patch with endogenous **fibrinogen** present in the blood exuding from the wound.

DETD . . . the GE patch in amounts effective for stimulating hemostasis, including, but not limited to: thrombin "T", an enzyme which converts **fibrinogen** to fibrin; calcium, sodium, magnesium or other ions that stimulate hemostasis; and optionally, **fibrinogen**, "F".

DETD The molecules "thrombin" and "**fibrinogen**" as defined herein are meant to include natural thrombin and **fibrinogen** molecules derived from an animal or human origin, a synthetic form or a recombinant form of the molecules, including functionally. . . use for safety reasons contains non-human thrombin, and preferred in this context is bovine thrombin. By avoiding use of human **fibrinogen** , risks associated with viral contamination of purified blood products (particularly with **fibrinogen**) are minimized. Indeed, the ingredients EACA, thrombin and GelFoam.RTM. all are approved by the U.S.
Food and Drug Administration for. . .

DETD . . . advantageously contains calcium ion and thrombin as well. It also is less expensive as compared with a patch that contains **fibrinogen**. Similar to the GE patch, the CAE patch can include additional hemostatic agents including, but not limited to, thrombin, calcium. . .

DETD . . . tripeptide RGD is composed of arginine, glycine and aspartic acid, and optionally serine "RGDS," and is the active site of **fibrinogen** and fibronectin. RGD accelerates wound healing and is believed to stimulate **fibroblast migration**.

DETD The RGD additive is also much less expensive than **fibrinogen**. RGD can be synthesized easily using conventional solid phase chemistry at a fraction of the cost of obtaining **fibrinogen**, which currently must be obtained by purification from a natural source.

CLM What is claimed is:
1. A dry sterile storage stable **fibrinogen**-free hemostatic patch comprising a biodegradable matrix selected from the group consisting of absorbable gelatin, calcium alginate, calcium/sodium elginate, collagen and. . .

L6 ANSWER 16 OF 17 USPATFULL

AB . . . a flexible sheet which conforms to the contour of the organ without the necessity of pre-moistening. The problem associated with thrombin-**fibrinogen** glues of adhesion of the wounded surface of the organ to adjacent tissue is avoided by applying the hemostatic agent. . .

SUMM . . . pastes containing coagulation-enhancing factors. One such coagulation enhancing substance employed to assist a cessation of bleeding or "hemostasis" is human **fibrinogen**, most commonly employed as a "fibrin glue".

SUMM Fibrin glue is composed of a mixture of human **fibrinogen** and bovine thrombin. It is sold as a kit containing separate vials of **fibrinogen** and thrombin solutions. These solutions are mixed together and applied to the wound in various ways, including as a paste,. . .

SUMM . . . of such solution, further hemorrhage occurs and the solutions are washed away by intense bleeding. Despite the headway made in **fibrinogen** compositions and surgical techniques, these pitfalls in achieving hemostasis underscore the need for development of a suitable product.

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DETD The RGD additive is also much less expensive than **fibrinogen**. RGD can be synthesized easily using conventional solid phase chemistry at a fraction of the cost of obtaining **fibrinogen**, which currently must be obtained by purification from a natural source.

L8 ANSWER 1 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:248362 CAPLUS
TITLE: The effect of interleukin-6 C/G-174 polymorphism and circulating interleukin-6 on fibrinogen plasma levels
AUTHOR(S): Margaglione, Maurizio; Bossone, Anna; Cappucci, Giuseppe; Colaizzo, Donatella; Grandone, Elvira; Di Minno, Giovanni
CORPORATE SOURCE: Unita di Aterosclerosi e Trombosi, I.R.C.C.S. "Casa Sollievo della Sofferenza", S. Giovanni Rotondo, Foggia, 71013, Italy
SOURCE: Haematologica (2001), 86(2), 199-204
CODEN: HAEMAX; ISSN: 0390-6078
PUBLISHER: Ferrata Storti Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 2 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:248361 CAPLUS
TITLE: In vitro measurement of platelet glycoprotein IIb/IIIa
receptor blockade by abciximab: Interindividual variation and increased platelet secretion
AUTHOR(S): Rossi, Francesca; Rossi, Eddardo; Pareti, Francesco I.; Colli, Susanna; Tremoli, Elena; Gallo, Luciana
CORPORATE SOURCE: Department of Pharmacologic Sciences, E. Grossi Paoletti Center, University of Milan, Milan, 20133, Italy
SOURCE: Haematologica (2001), 86(2), 192-198
CODEN: HAEMAX; ISSN: 0390-6078
PUBLISHER: Ferrata Storti Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 3 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:248180 CAPLUS
TITLE: Activation of the lectin complement pathway by ficolins
AUTHOR(S): Matsushita, Misao; Endo, Yuichi; Hamasaki, Naotaka; Fujita, Teizo
CORPORATE SOURCE: Department of Biochemistry, Fukushima Medical University School of Medicine, Fukushima, 960-1295, Japan
SOURCE: Int. Immunopharmacol. (2001), 1(3), 359-363
CODEN: IINMBA; ISSN: 1567-5769
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 4 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:247804 CAPLUS
TITLE: Zwitterionic SAMs that Resist Nonspecific Adsorption of Protein from Aqueous Buffer
AUTHOR(S): Holmlin, R. Erik; Chen, Xiaoxi; Chapman, Robert G.; Takayama, Shuichi; Whitesides, George M.
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Langmuir ACS ASAP

CODEN: LANGD5; ISSN: 0743-7463
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 5 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:245647 CAPLUS
TITLE: Antithrombotic therapy in the acute phase: New approaches
AUTHOR(S): Sherman, David G.
CORPORATE SOURCE: Department of Medicine (Neurology), University of Texas Health Science Center, San Antonio, TX, USA
SOURCE: Cerebrovasc. Dis. (Basel, Switz.) (2001), 11(Suppl. 1), 49-54
CODEN: CDISE7; ISSN: 1015-9770
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 6 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:245267 CAPLUS
TITLE: Hemostatic imbalance in active and quiescent ulcerative colitis
AUTHOR(S): van Bodegraven, Ad A.; Schoorl, Marianne; Baak, Jan P.
A.; Linskens, R. K.; Bartels, Piet C. M.; Tuynman, Hans A. R. E.
CORPORATE SOURCE: Departments of Gastroenterology and Histopathology, Medical Center Alkmaar and Academic Hospital Free University, Amsterdam, Neth.
SOURCE: Am. J. Gastroenterol. (2001), 96(2), 487-493
CODEN: AJGAAR; ISSN: 0002-9270
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 7 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:241550 CAPLUS
TITLE: Fibrin induces IL-8 expression from human oral squamous cell carcinoma cells
AUTHOR(S): Lalla, R. V.; Goralnick, S. J.; Tanzer, M. L.; Kreutzer, D. L.
CORPORATE SOURCE: Division of Oral Medicine, Department of Oral Diagnosis, University of Connecticut School of Dental Medicine, CT 06030, Farmington,, USA
SOURCE: Oral Oncol. (2001), 37(3), 234-242
CODEN: EJCCER; ISSN: 1368-8375
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 8 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:240930 CAPLUS
TITLE: Expression and characterization of t-PA in insect cells
AUTHOR(S): Liu, Jun Bo; Yang, Kai; Xue, Ai-Qun; Pang, Yi; Li, Bao
Jian
CORPORATE SOURCE: Biotechnology Research Center, Zhongshan University, Canton, 510275, Peop. Rep. China
SOURCE: Shiyan Shengwu Xuebao (2000), 33(4), 293-300
CODEN: SYSWAE; ISSN: 0001-5334
PUBLISHER: Shanghai Kexue Jishu Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

L8 ANSWER 9 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:238970 CAPLUS
TITLE: Binding mechanism of RGD and its mimetics to receptor GPIIb/IIIa. A theoretical study
AUTHOR(S): Suvire, F. D.; Rodriguez, A. M.; Mak, M. L.; Papp, J. G.; Enriz, R. D.
CORPORATE SOURCE: Department of Chemistry, National University of San Luis, Chacabuco 915 (5700), San Luis, Argent.
SOURCE: THEOCHEM (2001), 540(1-3), 257-270
CODEN: THEODJ; ISSN: 0166-1280
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 10 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:237079 CAPLUS
TITLE: Nuclear and mtDNA Phylogenies of the Trimeresurus Complex: Implications for the Gene versus Species Tree Debate
AUTHOR(S): Giannasi, Nicholas; Malhotra, Anita; Thorpe, Roger S.
CORPORATE SOURCE: School of Biological Sciences, University College of North Wales, Bangor, LL57 2UW, UK
SOURCE: Mol. Phylogenet. Evol. (2001), 19(1), 57-66
CODEN: MPEVEK; ISSN: 1055-7903
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 11 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:236478 CAPLUS
TITLE: Design and rationale of the ARBITER trial (arterial biology for the investigation of the treatment effects of reducing cholesterol)-a randomized trial comparing the effects of atorvastatin and pravastatin on carotid artery intima-media thickness
AUTHOR(S): Markwood, Thor T.; Kent, Steven M.; Coyle, Louis C.; Flaherty, Patrick J.; O'Malley, Patrick G.; Taylor, Allen J.
CORPORATE SOURCE: Cardiology and General Internal Medicine Services, Department of Medicine, Walter Reed Army Medical Center, Washington, DC, 20307-5001, USA
SOURCE: Am. Heart J. (2001), 141(3), 342-347
CODEN: AHJOA2; ISSN: 0002-8703
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 12 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:236169 CAPLUS
TITLE: Administration of abciximab to patients receiving tirofiban or eptifibatide: Effect on platelet function
AUTHOR(S): Lev, Eli I.; Osende, Julio I.; Richard, Merwin F.; Robbins, Jonathan A.; Delfin, Jenny A.; Rodriguez, Oswaldo; Sharma, Samin K.; Jayasundera, Tim; Badimon, Juan J.; Marmur, Jonathan D.
CORPORATE SOURCE: The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA
SOURCE: J. Am. Coll. Cardiol. (2001), 37(3), 839-846
CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal

LANGUAGE: English

L8 ANSWER 13 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:234414 CAPLUS
TITLE: Clinical utility of LDL-apheresis in the treatment of sudden hearing loss: a prospective, randomized study
AUTHOR(S): Suckfull, Marcus; Thiery, Joachim; Schorn, Karin; Kastenbauer, Ernst; Seidel, Dietrich
CORPORATE SOURCE: Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Grosshadern, Ludwig-Maximilians-University Munich, Munich, Germany
SOURCE: Acta Oto-Laryngol. (1999), 119(7), 763-766
CODEN: AOLAAJ; ISSN: 0001-6489
PUBLISHER: Scandinavian University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 14 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:233282 CAPLUS
TITLE: Laboratory diagnosis of hemostatic system status
AUTHOR(S): Platonova, T. M.; Chernishenko, T. M.; Gornits'ka, O. V.; Savchuk, O. M.; Sokolovs'ka, L. I.; Gamisoniya, M.
Sh.; Makogonenko, E. M.
CORPORATE SOURCE: Inst. Biokhim. im. O. V. Palladina, NAN Ukraini, Kiev,
Ukraine
SOURCE: Ukr. Biokhim. Zh. (2000), 72(6), 67-73
CODEN: UBZKAA
PUBLISHER: Institut Biokhimii im. O. V. Palladina NAN Ukraini
DOCUMENT TYPE: Journal
LANGUAGE: Ukrainian

L8 ANSWER 15 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:232379 CAPLUS
TITLE: A New Human Hereditary Amyloidosis: The Result of a Stop-Codon Mutation in the Apolipoprotein AII Gene
AUTHOR(S): Benson, Merrill D.; Liepnieks, Juris J.; Yazaki, Masahide; Yamashita, Taro; Hamidi Asl, Kamran; Guenther, Brian; Kluve-Beckerman, Barbara
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, 46202, USA
SOURCE: Genomics (2001), 72(3), 272-277
CODEN: GNMCEP; ISSN: 0888-7543
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 16 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:231324 CAPLUS
TITLE: Coagulation and sepsis
AUTHOR(S): Christopoulou-Cokkinou, V.
CORPORATE SOURCE: Haematologic Lab., Evangelismos Hospital, Athens, Greece
SOURCE: Delt. Ell. Mikrobiol. Etair. (2000), 45(2), 150-159
CODEN: DHMHDW; ISSN: 0438-9573
PUBLISHER: Ellenike Mikrobiologike Etaireia
DOCUMENT TYPE: Journal
LANGUAGE: Greek

L8 ANSWER 17 OF 18400 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:228719 CAPLUS
TITLE: Novel pharmacological activities of Curcuma longa extracts
INVENTOR(S): Quintanilla Almagro, Eliseo; Ramirez Bosca, Ana;

Bernd, August; Pardo Zapata, Jose; Diaz Alperi, Joaquin; Pamies Mira, David; Carrion Gutierrez, Miguel
Angel; Sempere Ortells, Jose Miguel
PATENT ASSIGNEE(S): Asac Compania de Biotecnologia e Investigacion, S.A., Spain
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021185	A1	20010329	WO 2000-ES354	20000921

W: AU, CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

ATFULL

DETD . . . Sci., 26:457-463 (1985)). They are generally high molecular weight (>150,000 daltons) fibrinous glycoproteins, which include collagens, vitronectin, elastin, laminin, actin, **fibrinogen**, and other ECM materials. Biologically active fragments or analogs of such proteins can also be used.

DETD In preparing the **wound**-healing dressing, the fibronectin and, optionally, other protein such as albumin is reacted with the salt or acid or base in. . .

DETD In an alternative method for preparing a **wound**-dressing of the invention, an aqueous solution of fibronectin and optionally, other protein such as albumin, at a concentration from about. . .

DETD . . . fibronectin polymer exerts a number of beneficial effects on the wound-healing response. Fibronectin is a chemotactic material which induces the **migration** of **fibroblasts** or, in the case of corneal tissue, **fibroblast**-like cells known as keratocytes into the wound site. These cells are known to deposit a number of wound-healing substances. Furthermore,. . .

AN 90:90979 USPATFULL

PI US 4973466 19901127

TI Wound-healing dressings and methods

L11 ANSWER 23 OF 34 USPATFULL

DETD . . . of collagen which leads to the formation of scar tissue. The topical addition of hyaluronic acid and fibronectin in the **wound** bed will alter the adult healing process and facilitate accelerated healing and reduce the formation of scar tissue.

DETD Test results all support the conclusion that human **fibrinogen** specifically binds hyaluronic acid and show the feasibility of the role of these two macromolecules in **wound** healing. The hyaluronic-**fibrinogen** interaction may be important or even necessary for successful **wound** healing, Paul H. Weigel, Stephen J. Front, Robert D. LeBoeuf, and Cad T. McGary, The Specific Interaction between Fibrin(ogen) and Hyaluronan: Possible Consequences of Hemostasis, Inflammation and **Wound** Healing, The Biology of Hyaluronan, Wiley-Interscience Publications, Ciba Foundation Symposium 143, 1989, pp 248-285.

DETD Table II is the result of research performed by Frederick Ginnell, Fibronectin and **Wound** Healing, reported in the Journal of Cellular Biochemistry 26, pp

DETD TABLE II

L11 ANSWER 12 OF 34 USPATFULL

DETD . . . material is below about 20 .mu.m, more preferably below 5 .mu.m, and most preferably below about 1 .mu.m, to prevent **fibroblasts** from intruding or penetrating. As noted above, in the course of normal **wound** closure, **fibroblasts** **migrate** into the fibrin clot network and the developing granulation tissue, where they produce i.e., collagen and thus contribute to the. . .

DETD It is well known that thrombin acts as a protease which will cleave fibrino peptide A and B from the **fibrinogen** molecule and convert it into fibrin. It is desirable that all of the **fibrinogen** be converted into fibrin, as residual amounts of **fibrinogen** may lead to adhesion formation upon reacting with thrombin provided by the body. The rate of the conversion of **fibrinogen** into fibrin increases as the concentration of thrombin increases, provided that there is a sufficient quantity of **fibrinogen** present. Preferably, thrombin is added at a ratio of 7 parts by weight for every 1 part by weight of **fibrinogen**, and more preferably within the range of 6 to 1 a more preferably within the range of 4 to 1. . . a fibrin film with a relatively large pore size. The large pore size fibrin film is suitable for hemostasis and **wound** healing. Accordingly, in still further embodiments of the present invention, the fibrin film further comprises less than 5% by weight of **fibrinogen**, preferably less than 4% by weight of **fibrinogen**, preferably less than 3% by weight of **fibrinogen**, preferably less than 2% by weight of **fibrinogen**, and most preferably less than 1% by weight of **fibrinogen**, in terms of the total dry weight of the **fibrinogen** plus fibrin each time.

DETD Generally speaking, the lower the amount of residual **fibrinogen** , the better the non-adhesive properties of the fibrin film, since **fibrinogen** in vivo may promote fibrin formation and thus adhesion formation. For the purpose of determining the fibrin and the **fibrinogen** content of the fibrin film, the methods of SDS-Page (SDS-Gelelectrophoresis) may be used.

DETD . . . promoters, preferably in an amount up to 1% by weight in terms of the total dry weight of fibrin plus **fibrinogen**. Examples of fibrinolytic agents include t-PA, .mu.-PA, streptokinase, staphylokinase, plasminogen and the like. These compounds promote fibrinolysis and thus can. . .

DETD . . . from another, to prevent the formation of adhesions. The method comprises the steps of: (1) providing a liquid solution of **fibrinogen**; (2) providing a liquid solution of thrombin having a concentration from 3-10,000 IU/ml and more preferably from 200-500 IU/ml; (3) providing a spray unit in fluid communication with the **fibrinogen** and thrombin solutions, the spray unit being capable of separately atomizing the **fibrinogen** and the thrombin into an aerosol with an energy selected from the group consisting of liquid energy, mechanical energy, vibration energy, and electric energy; (4) spraying the **fibrinogen** solution onto the surface with the spray unit; (5) spraying the thrombin solution separately from the **fibrinogen** solution onto the surface; and (6) mixing for the first time the **fibrinogen** with the thrombin on the surface to make a fibrin film, in situ. The film is capable of preventing the. . .

DETD . . . the main determinants in influencing the fibrin network structure and its biological and biophysical characteristics include the concentrations of thrombin, **fibrinogen** and factor XIII, and, of course, the temperature at which the polymerization is performed. The **fibrinogen** concentration and, in a large measure, the clottable protein concentration is proportional to the tensile strength, while the concentration of. . .

DETD . . . the same regular and uniform structure at each concentration of thrombin. At low concentrations of thrombin, there is a slow

fibrinogen conversion associated with a slow fiber growth, thus leading to the formation of a fibrin structure with thick fibers and. . . of cells drastically opens the three-dimensional structure of the network. Such an opened and irregular structure is physiologically favorable to **fibroblast migration** into the fibrin clot network during the normal **wound** healing process. It is apparent from the figures that by varying the thrombin concentration, fibrin networks with low or high. . .

DETD . . . highly ordered structure having "relatively large pores" as a matrix for cells and molecules for the achievement of hemostasis and **wound** repair.

DETD Under consideration of these three factors, in certain embodiments hemostasis and **wound** repair is addressed by applying a single layer of fibrin glue to the injury site(s), while the separation/isolation of the. . . inventors have discovered that an important parameter to be taken into account in using such a combination of a hemostatic agent/**wound** repair promoter and a bio-mechanical barrier is the time required for complete conversion of **fibrinogen** to fibrin. Specifically, it has been found that the layer of the fibrin glue and respectively the last layer, if more than one layer is applied to an injured surface, should be allowed to set until the conversion of **fibrinogen** to fibrin is complete. By way of example, when fibrin glue is applied simultaneously to two injured surfaces such as. . . in order to form a single layer each time, and the surfaces come into contact with each other before the **fibrinogen**-fibrin conversion is complete, it may occur that these surfaces are glued together, i.e., that adhesions are formed.

DETD . . . propose to allow undisturbed setting after application of the respective last external layer of fibrin glue until the conversion of **fibrinogen** to fibrin is complete. This does not apply to the fibrin film of the invention, since this is allowed to. . . thus apparently also a matter of clinical experience. However, in vitro methods are known in the art for monitoring the **fibrinogen** -fibrin conversion. By way of example this can be followed by monitoring turbidity which is the measure of the optical density. . .

DETD . . . upon application of the first fibrin glue. Preferably the first fibrin glue has been made by mixing of the above-described **fibrinogen**-containing solution with an equal volume or a thrombin-containing solution comprising less than 1000 IU thrombin, preferably less than 150 IU. The fibrin glue has been preferably made by mixing said **fibrinogen**-containing solution with an equal volume of a thrombin-containing solution of at least 50 IU thrombin, preferably of at least 150. . .

DETD . . . between two injured surfaces, acts as a bio-mechanical barrier. The fibrin glue is preferably produced by mixing of a first, **fibrinogen**-containing solution with an equal volume of a thrombin-containing solution comprising preferably 1-300 IU/ml thrombin, preferably at least 20 IU/ml thrombin. . .

AN 1999:150320 USPATFULL

PI US 5989215 19991123

TI Fibrin delivery device and method for forming fibrin on a surface

L4 158436 MIGRATION?

=> s migrat?
L5 231870 MIGRAT?

=> s s l4 or l5
MISSING OPERATOR S L4
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l4 or l5
L6 231870 L4 OR L5

=> s l3 (1p) l6
L7 4035 L3 (1P) L6

=> s l7 (5p) wound?
L8 944 L7 (5P) WOUND?

=> s l3 (30a) l6
L9 1745 L3 (30A) L6

=> s l9 (3p) wound?
L10 500 L9 (3P) WOUND?

=> s l10 (3p) l2
L11 34 L10 (3P) L2

=> d 1-34 kwic, an, pi, ti

L11 ANSWER 1 OF 34 USPATFULL
SUMM The present invention relates to topical dosage formulations, containing human plasma fibronectin and other **wound** healing promoters, for use in promoting **wound** healing in humans. In particular, the invention relates to the healing of chronic venous ulcers. A deepithelialized skin cell diffusion. . .
SUMM . . . binding glycoprotein. These names reflect biological activities of fibronectin such as cell recruitment, opsonization of particulate debris, and promotion of **wound** contraction. Reviews on structure and activities of fibronectin have been published elsewhere.sup.2,3.
SUMM **Wound** healing is usually divided into three phases: the inflammatory phase, the proliferative phase, and the remodeling phase. Fibronectin has been reported to be involved in each stage of the **wound** healing process, particularly by creating a scaffold to which the invading cells can adhere. Initially, many mediators, such as fibronectin and **fibrinogen**, are released to the **wound** site. Fibronectin promotes inflammatory cells migration into the **wound** and debris phagocytosis by the monocytes. Thereafter, angiogenesis and reepithelialization take place. At this stage fibronectin exerts chemotactic activity on endothelial cells, and promotes the **migration** of epithelial cells and **fibroblasts** onto the basal membrane. Fibronectin also appears to be an essential component of the remodeling phase where it plays a. . . organization of collagen fibrils. The fibrillar collagen ultimately forms fibrous bundles that greatly enhance the tissue tensile strength, leading to **wound** closure.
SUMM Topically applied plasma fibronectin has been reported as being useful for increasing the rate of **wound** healing such as in corneal **wounds**.sup.4,5 and leg ulcers.sup.6. However, no one has described a suitable topical carrier for use in treating **wounds** that can ensure the delivery of an effective amount of fibronectin. A major limiting factor in developing an effective topical. . . (cream, ointment, gel, etc.) into the site of delivery (which in the case of the

present invention is a skin **wound**). Very active drugs, such as growth factors, may have no therapeutic value if the topical formulation does not allow the drug to move from the semi-solid carrier into the **wound**. Therefore, it would be highly desirable to develop a formulation which would maximize the contact time of the fibronectin with the **wound** and also control the release of fibronectin to the **wound**, thereby leading to high absorption values. The present invention provides such delivery system in the form of aqueous gels and. . .

SUMM . . . invention provides aqueous gel formulations and one cream formulation containing fibronectin and their use for the delivery of an effective **wound** healing amount of fibronectin to a **wound** site. The gel formulation comprises a water soluble, pharmaceutically acceptable polymer which is prepared from an effective amount of fibronectin.. . .

AN 2001:97882 USPATFULL

PI US 6251859 B1 20010626

TI Deepithelialized skin diffusion cell system

L11 ANSWER 2 OF 34 USPATFULL

SUMM Basic **fibroblast** growth factor (FGF-2) is a potent stimulator of angiogenesis and the **migration** and proliferation of **fibroblasts** (see, for example, Gospodarowicz et al., Mol. Cell. Endocinol. 46:187-204 (1986) and Gospodarowicz et al., Endo. Rev. 8:95-114 (1985)). Acidic **fibroblast** growth factor (FGF-1) has been shown to be a potent angiogenic factor for endothelial cells (Burgess et al., supra, 1989).. . .

SUMM . . . for such inconsistent results are not known, but might be the result of difficulty in applying growth factors to a **wound** in a manner in which they can exhibit their normal array of biological activities. For example, it appears that some. . . J. Cell Physiol. 154:152-161 (1993)). Because of such inconsistent results, the role played by exogenously applied growth factors in stimulating **wound** healing is not clear. Further, a means by which growth factors might be applied to **wounds** to produce prolonged contact between the **wound** and the growth factor(s) is not presently known.

SUMM FGs generally are prepared from: (1) a **fibrinogen** concentrate, which contains fibronectin, Factor XIII, and von Willebrand factor; (2) dried human or bovine thrombin; and (3) calcium ions. Commercially prepared FGs generally contain bovine components. The **fibrinogen** concentrate can be prepared from plasma by cryoprecipitation followed by fractionation, to yield a composition that forms a sealant or clot upon mixture with thrombin and an activator of thrombin such as calcium ions. The **fibrinogen** and thrombin concentrates are prepared in lyophilized form and are mixed with a solution of calcium chloride immediately prior to. . . coagulate on the tissue surface and form a clot that includes cross-linked fibrin. Factor XIII, which is present in the **fibrinogen** concentrate, catalyzes the cross-linking.

AN 2001:32823 USPATFULL

PI US 6197325 B1 20010306

TI Supplemented and unsupplemented tissue sealants, methods of their production and use

L11 ANSWER 3 OF 34 USPATFULL

SUMM Many attempts have been made to produce a composition which can be used to facilitate **wound** repair. Many of these compositions involve collagen as a component. U.S. Pat. Nos. 4,950,483 and 5,024,841 each discuss the usefulness of collagen implants as **wound** healing matrices. U.S. Pat. No. 4,453,939 discusses a **wound** healing composition of collagen with a **fibrinogen** component and a thrombin component, and optionally fibronectin. U.S. Pat. No. 4,970,298 discusses the usefulness of a biodegradable collagen matrix (of collagen, hyaluronic acid, and fibronectin) for **wound** healing.

Yamada et al. (1995) disclose an allogeneic cultured dermal substitute that is prepared by plating fibroblasts onto a spongy. . .

SUMM . . . a component. Ortonne (1996), Borgognoni et al. (1996), and Nakamura et al. (1997) each discuss the usefulness of HA for **wound** healing. In Nakamura et al. (1997), the HA was combined with chondroitin sulfate in one series of experiments. In U.S.. . . uric acid, urea, sodium, potassium, chloride and magnesium to create a moist healing environment that simulates the fetal in utero **wound** healing matrix. U.S. Pat. No. 5,631,011 discloses a composition of HA and fibrin or **fibrinogen**.

SUMM Various other compositions have also been explored for their **wound** healing capabilities. Kratz et al. (1997) used a gel of heparin ionically linked to chitosan. Bartold and Raben (1996) studied platelet-derived growth factor (PDGF). Henke et al. (1996) disclosed that chondroitin sulfate proteoglycan mediated cell migration on **fibrinogen** and invasion into a fibrin matrix, while Nakamura et al. (1997) concluded that chondroitin sulfate did not affect **wound** closure in a corneal epithelial **wound**. Henke et al. (1996) also disclosed that an anti-CD44 antibody blocked endothelial cell migration on **fibrinogen**. U.S. Pat. No. 5,641,483 discloses topical gel and cream formulations containing human plasma fibronectin for healing of cutaneous **wounds**. Schultz et al. (1992) disclose a composition of epidermal growth factor (EGF), fibronectin, a synthetic collagenase inhibitor, and Aprotinin.

SUMM Various studies involving fibronectin (FN) and/or particular fibronectin peptides and **wound** healing have also been reported. Many of these studies involve the RGD sequence, part of the cell binding domain of. . . 1992; Kishida et al. 1992). Schor et al. (1996) disclose that only the gelatin binding domain of FN (GBD) stimulates **fibroblast migration** into a 3-D matrix of native type I collagen fibrils at femtomolar concentrations; whereas peptides of the other FN functional domains do not stimulate **fibroblast migration** in this assay at femtomolar to nanomolar concentrations. Schor et al. (1996) also disclose that the RGDS-containing cell binding domain of FN does, however, stimulate **fibroblast migration** in the transmembrane (or "Boyden chamber") assay. Steed et al. (1995) disclose that the RGD peptide matrix (known as Argidene Gel.TM. or as Telio-Derm Gel.TM.) promoted **wound** healing. On the contrary, Sponsel et al. (1994) disclose that an RGD peptide impaired healing of a mechanical **wound** made in a confluent monolayer of one epithelial cell line. Kartha and Toback (1992) also concluded that an RGDS peptide completely inhibited cell migration into a **wound** area. Kishida et al. (1992), however, disclose that an RGD-albumin conjugate adsorbed onto a polyurethane sponge exhibited tissue ingrowth-promoting activity.

SUMM Other portions of FN have also been studied for **wound** healing activity. U.S. Pat. No. 5,198,423 studied the effects of a polypeptide containing a cell binding domain and a heparin binding domain of FN on **wound** healing. U.S. Pat. No. 4,589,881 studied the effects of a 108 aa polypeptide fragment of FN on **wound** healing, as well as a biologically active fragment thereof. Sponsel et al. (1994) studied the effect of the tetrapeptide REDV and the peptide LDVPS on **wound** healing.

SUMM The severity of the problem of chronic, nonhealing **wounds** dictates that continual efforts be made to define new and more effective matrices and methods for facilitating **wound** healing.

DETD Assay plates are prepared as described under **fibroblast migration** assays. The assay for measuring **fibroblast** adhesion to matrix proteins are performed essentially as described (Gailit et al. 1993) except that the cell concentration is lowered. . .

DETD Assay of **Wound** Healing

DETD . . . Surrounding the collagen gel, or dermal equivalent, with a fibrin clot produces a simple inside-outside model of the early

cutaneous **wound** (FIG. 1). Without an added stimulus, no more than a few of the normal adult human dermal **fibroblasts** within the collagen gel would **migrate** into the fibrin gel. However, the transmigration of **fibroblasts** from the collagen gel into the fibrin gel is enhanced by the replacement of the fibrin gel with the extracellular. . . by the addition of the extracellular matrix to the fibrin gel, since the extracellular matrix facilitates cell movement thereby enhancing **wound** healing.

DETD Fibronectin (FN) is required for **fibroblast migration** through both fibrin clots and hyaluronic acid (HA) gels. Initially, experiments were conducted to determine whether FN, either in a fibrin gel or in a collagen gel, is required for **fibroblast** transmigration. To do this, FN was selectively removed from each matrix material. First, residual FN was removed from the **fibrinogen** preparation by affinity chromatography on gelatin. After removal of FN, fibroblast transmigration into the fibrin clot was decreased by about. . . be restored by the addition of FN to the fibrin gel. Optimal cell movement was observed with 30 .mu.g/ml, a FN:**fibrinogen** ratio of 1:10, the physiological plasma ratio. In FIG. 10A, migration induced by 30 ng/ml PDGF-BB (shaded bars; open bars: 0 ng/ml PDGF) was measured under the usual assay conditions. The **fibrinogen** preparation used to form the fibrin gel was untreated (left), treated with gelatin-Sepharose to remove FN (center), or treated with. . .

DETD . . . conditions. Contraction of the collagen gel was stimulated with serum as usual (FBS) or with 30 ng/ml PDGF-BB (PDGF). The **fibrinogen** preparation used to form the fibrin gel was untreated (Fb), treated with gelatin-Sepharose to remove FN (Fb-FN), or treated with. . .

AN 2001:29530 USPATFULL

PI US 6194378 B1 20010227

TI Fibronectin peptides-based extracellular matrix for wound healing

L11 ANSWER 4 OF 34 USPATFULL

SUMM Other core materials include collagen (U.S. Pat No 4,495,288, Jarvis, A. P. et al.), agar, agarose, **fibrinogen** (U.S. Pat. No. 4,647,536, Mosbach, K., et al.), and fibronectin or laminin (U.S. Pat. No. 4,902,295, Walthall, B. J., et. . .

SUMM . . . that its structural characteristics are similar to the glycosaminoglycan components of naturally occurring extra-cellular matrix. In the presence of chitosan, **fibroblasts** and mesenchymal vascular cells in the surrounding tissue were stimulated to **migrate**, proliferate, and differentiate. These cellular activities are essential components of **wound** healing and tissue-rebuilding. Chitosan has also been reported to be effective in bone-repair and as a suture material (Sapelli. P.. . .

AN 2000:146135 USPATFULL

PI US 6140089 20001031

TI Chitosan core matrix containing cells encapsulated in a thermoplastic semipermeable membrane

L11 ANSWER 5 OF 34 USPATFULL

SUMM Basic **fibroblast** growth factor (FGF-2) is a potent stimulator of angiogenesis and the **migration** and proliferation of **fibroblasts** (see, for example, Gospodarowicz et al., Mol. Cell. Endocinol. 46:187-204 (1986) and Gospodarowicz et al., Endo. Rev. 8:95-114 (1985)). Acidic **fibroblast** growth factor (FGF-1) has been shown to be a potent angiogenic factor for endothelial cells (Burgess et al., supra, 1989).. . .

SUMM . . . for such inconsistent results are not known, but might be the result of difficulty in applying growth factors to a **wound** in a manner in which they can exhibit their normal array of biological activities. For example, it appears that some. . . J. Cell Physiol. 154:152-161 (1993)). Because of such inconsistent results, the role played by exogenously applied growth factors in stimulating

wound healing is not clear. Further, a means by which growth factors might be applied to **wounds** to produce prolonged contact between the **wound** and the growth factor(s) is not presently known.

SUMM FGs generally are prepared from: (1) a **fibrinogen** concentrate, which contains fibronectin, Factor XIII, and von Willebrand factor; (2) dried human or bovine thrombin; and (3) calcium ions. Commercially prepared FGs generally contain bovine components. The **fibrinogen** concentrate can be prepared from plasma by cryoprecipitation followed by fractionation, to yield a composition that forms a sealant or clot upon mixture with thrombin and an activator of thrombin such as calcium ions. The **fibrinogen** and thrombin concentrates are prepared in lyophilized form and are mixed with a solution of calcium chloride immediately prior to. . . coagulate on the tissue surface and form a clot that includes cross-linked fibrin. Factor XIII, which is present in the **fibrinogen** concentrate, catalyzes the cross-linking.

AN 2000:121069 USPATFULL

PI US 6117425 20000912

TI Supplemented and unsupplemented tissue sealants, method of their production and use

L11 ANSWER 6 OF 34 USPATFULL

SUMM For systems where the matrix is made of fibrin, particulates may be incorporated directly into the **fibrinogen** component which is obtained in lyophilized form. The particulates may be alginate, gelatin, polyethylene glycol, polylactic acid/polyglycolic acid (PLA/PGA) hollow. . .

SUMM . . . be preformed and used for surgical reconstruction and drug delivery. In a particular embodiment, the implant is applied to the **wound** site as a dressing. The matrix material may be fibrin, alginate, collagen, PLA/PGA or other biocompatible polymers as well as. . .

SUMM . . . of pores to permit tissue and fluid influx into the matrix. The matrix then acts as a scaffolding for the **migrating** cells (e.g. macrophages, **fibroblasts**, and neovascular endothelial cells) and will degrade as these cells express connective tissue components for remodeling and regeneration.

AN 2000:113513 USPATFULL

PI US 6110484 20000829

TI Collagen-polymer matrices with differential biodegradability

L11 ANSWER 7 OF 34 USPATFULL

DETD . . . the discovery of the requirement for the integrin .beta.3 subunit for carcinoma cells to spread or migrate on Vn (and **fibrinogen**) (Leavesley, D. I. J. Cell Biol. 117:1101-1107 (1992)). A human pancreatic carcinoma was found to use integrin .alpha..sub.v .beta.5 as. . . heterodimer providing these cells with novel adhesive and biological properties, namely the capacity to attach and spread on Vn or **fibrinogen** with .beta..sub.3 localization to focal contacts. These cells gained the capacity to migrate through a porous membrane in response to either Vn or **fibrinogen**. These results demonstrated that the .beta..sub.3 and .beta..sub.5 integrin subunits, when associated with .alpha..sub.V, promote distinct cellular responses to a. . .

DETD . . . angiogenesis was shown by Brooks, P. C. et al., Science 264:569-571 1994). This VnR was expressed on blood vessels in **wound** granulation tissue and increased in expression during angiogenesis. An antibody to .alpha..sub.V .beta..sub.3 blocked angiogenesis induced by cytokines, growth factors. . .

DETD **Wound** healing requires a coordinated influx of fibroblasts, vascular endothelium and epithelium. Agents which promote a more rapid influx of fibroblasts, endothelial and epithelial cells into **wounds** should increase the rate at which **wounds** heal. However, such stimulation may also result in unwanted tissue fibrosis

and scarring. The PAI-1 mutants of the present invention preferably applied topically are useful in downregulating the influx of, for example, fibroblasts into a **wound**. Judicious use of these proteins will allow a balance to be achieved between **wound** healing and fibrosis or scarring.

DETD Fibrosis in the lung is a major problem in chemotherapy with agents such as bleomycin and adriamycin. **Fibroblasts migrate** into the lung tissue (or other chronically inflamed tissue) on a fibrin matrix and lay down collagen. Endogenous PAI-1 bound. . . fibrosis in other chronically inflamed tissues involves increases in tissue factor which stimulates prothrombin activation to thrombin which results in **fibrinogen** conversion to fibrin and fibrin deposition. Inflammation also upregulates PAI-1. However, cells such as **fibroblasts** are able to displace PAI-1 in binding to and **migrating** along the fibrin matrix. Ultimately, their **migration** and secretion of collagen results in fibrosis. The PAI-1 mutant protein of this invention are used to disrupt this process by inhibiting the cell:matrix interaction and inhibiting **fibroblast migration** and generation of fibrosis in the lung or any other chronically inflamed tissue. The protein may be administered as an. . .

AN 2000:105683 USPATFULL

PI US 6103498 20000815

TI Mutant plasminogen activator-inhibitor type 1 (PAI-1) and uses thereof

L11 ANSWER 8 OF 34 USPATFULL

SUMM . . . embodiments, the pore size of the barrier material is below about 5 .mu.m, preferably below about 1 .mu.m, to prevent **fibroblasts** from intruding or penetrating. As noted above, in the course of normal **wound** closure, **fibroblasts migrate** into the fibrin clot network and the developing granulation tissue, where they produce i.a. collagen and thus contribute to the. . .

SUMM In still further embodiments of the present invention, the fibrin film further comprises less than 5% by weight of **fibrinogen**, preferably less than 4% by weight of **fibrinogen**, preferably less than 3% by weight of **fibrinogen**, preferably less than 2% by weight of **fibrinogen**, and most preferably less than 1% by weight of **fibrinogen**, in terms of the total dry weight of the **fibrinogen** plus fibrin each time. The fibrin film of the invention is usually made by catalytic conversion of **fibrinogen** to fibrin. Generally speaking, the lower the amount of residual **fibrinogen**, the better the non-adhesive properties of the fibrin film, since **fibrinogen** in vivo may promote fibrin formation and thus adhesion formation. Ideally, the **fibrinogen** to fibrin conversion should be complete, i.e., the fibrin film contains no residual **fibrinogen**. For the purpose of determining the fibrin and the **fibrinogen** content of the fibrin film, the methods of SDS-Page (SDS-Gelelectrophoresis) may be used.

SUMM . . . the main determinants in influencing the fibrin network structure and its biological and biophysical characteristics include the concentrations of thrombin, **fibrinogen** and factor XIII, and, of course, the temperature at which the polymerization is performed. The **fibrinogen** concentration and, in a large measure, the clottable protein concentration is proportional to the tensile strength, while the concentration of. . .

SUMM . . . the same regular and uniform structure at each concentration of thrombin. At low concentrations of thrombin, there is a slow **fibrinogen** conversion associated with a slow fiber growth, thus leading to the formation of a fibrin structure with thick fibers and. . . of cells drastically opens the three-dimensional structure of the network. Such an opened and irregular structure is physiologically favorable to **fibroblast migration** into the fibrin clot network during the normal **wound** healing process. It is

apparent from the figures that by varying the thrombin concentration, fibrin networks with low or high. . .

SUMM . . . highly ordered structure having `relatively large pores` as a matrix for cells and molecules for the achievement of hemostasis and **wound** repair.

SUMM Under consideration of these three factors, in certain embodiments haemostasis and **wound** repair is addressed by applying a single layer of fibrin glue to the injury site(s), while the separation/isolation of the. . . inventors have discovered that an important parameter to be taken into account in using such a combination of a haemostatic agent/**wound** repair promoter and a bio-mechanical barrier is the time required for complete conversion of **fibrinogen** to fibrin. Specifically, it has been found that the layer of the fibrin glue and respectively the last layer, if more than one layer is applied to an injured surface, should be allowed to set until the conversion of **fibrinogen** to fibrin is complete. By way of example, when fibrin glue is applied simultaneously to two injured surfaces such as. . . in order to form a single layer each time, and the surfaces come into contact with each other before the **fibrinogen**-fibrin conversion is complete, it may occur that these surfaces are glued together, i.e., that adhesions are formed.

SUMM . . . propose to allow undisturbed setting after application of the respective last external layer of fibrin glue until the conversion of **fibrinogen** to fibrin is complete. This does not apply to the fibrin film of the invention, since this is allowed to. . . thus apparently also a matter of clinical experience. However, in vitro methods are known in the art for monitoring the **fibrinogen** -fibrin conversion. By way of example this can be followed by monitoring turbidity which is the measure of the optical density. . .

SUMM . . . upon application of the first fibrin glue. Preferably the first fibrin glue has been made by mixing of the above-described **fibrinogen**-containing solution with an equal volume of a thrombin-containing solution comprising less than 1000 IU thrombin, preferably less than 150 IU. The fibrin glue has been preferably made by mixing said **fibrinogen**-containing solution with an equal volume of a thrombin-containing solution of at least 50 IU thrombin, preferably of at least 150. . .

SUMM . . . between two injured surfaces, acts as a bio-mechanical barrier. The fibrin glue is preferably produced by mixing of a first, **fibrinogen**-containing solution with an equal volume of a thrombin-containing solution comprising 1-300 IU/ml thrombin, preferably at least 20 IU/ml thrombin and. . .

AN 2000:73929 USPATFULL

PI US 6074663 20000613
WO 9622115 19960725

TI Method of using cross-linked fibrin material

L11 ANSWER 9 OF 34 USPATFULL

SUMM Basic **fibroblast** growth factor (FGF-2) is a potent stimulator of angiogenesis and the **migration** and proliferation of **fibroblasts** (see, for example, Gospodarowicz et al., Mol. Cell. Endocinol. 46:187-204 (1986) and Gospodarowicz et al., Endo. Rev. 8:95-114 (1985)). Acidic **fibroblast** growth factor (FGF-1) has been shown to be a potent angiogenic factor for endothelial cells (Burgess et al., supra, 1989).. . .

SUMM . . . for such inconsistent results are not known, but might be the result of difficulty in applying growth factors to a **wound** in a manner in which they can exhibit their normal array of biological activities. For example, it appears that some. . . J. Cell Physiol. 154:152-161 (1993)). Because of such inconsistent results, the role played by exogenously applied growth factors in stimulating **wound** healing is not clear. Further, a means by which growth factors might be applied to **wounds** to produce prolonged contact between the **wound** and the growth factor(s) is not

presently known.

SUMM FGs generally are prepared from: (1) a **fibrinogen** concentrate, which contains fibronectin, Factor XIII, and von Willebrand factor; (2) dried human or bovine thrombin; and (3) calcium ions. Commercially prepared FGs generally contain bovine components. The **fibrinogen** concentrate can be prepared from plasma by cryoprecipitation followed by fractionation, to yield a composition that forms a sealant or clot upon mixture with thrombin and an activator of thrombin such as calcium ions. The **fibrinogen** and thrombin concentrates are prepared in lyophilized form and are mixed with a solution of calcium chloride immediately prior to. . . coagulate on the tissue surface and form a clot that includes cross-linked fibrin. Factor XIII, which is present in the **fibrinogen** concentrate, catalyzes the cross-linking.

AN 2000:50372 USPATFULL

PI US 6054122 20000425

TI Supplemented and unsupplemented tissue sealants, methods of their production and use

L11 ANSWER 10 OF 34 USPATFULL

SUMM For example, **fibrinogen** being present in plasma interacts with a platelet membrane glycoprotein complex IIb/IIIa via RGD to cause a platelet aggregation, and it is considered that a synthetic peptide having RGD inhibits the interaction between **fibrinogen** and a platelet membrane glycoprotein complex IIb/IIIa and hence, it is useful as a platelet aggregation inhibitor [Phillips, D. R.,. . .

SUMM . . . differentiation and growth of cells [Yamada, K. M., et al., Ann. Rev. Biochem., 52, 761 (1983)], but since it stimulates **migration** of **fibroblast** and macrophage, it is expected to be applied to the treatment of **wound** or the regulation of immune mechanism. Particularly, fibronectin has been tried in the local treatment of corneal disorders by utilizing the promotion effect thereof on **wound** healing [Fujikawa, L. S., et al., Lab. Invest., 45, 120 (1981)].

AN 2000:44094 USPATFULL

PI US 6048854 20000411

TI 2,3-diaminopropionic acid derivative

L11 ANSWER 11 OF 34 USPATFULL

DETD A number of anti-thrombotic agents are currently known which inhibit clot formation by preventing platelet integrins from binding **fibrinogen** or fibronectin. These anti-thrombotics, however, rely on competitive inhibition to prevent platelet integrins from binding to **fibrinogen** or fibronectin. In this manner, large doses of these agents are required to achieve the desired anti-thrombotic affect.

DETD As noted above, it is contemplated that PHSRN SEQ ID NO.:1 antagonists may depress **wound** healing. This expectation is based on the discovery that PHSRN (SEQ ID NO.:1)-containing peptides promote **wound** healing.

DETD . . . basement membranes in vitro in the presence of serum or under serum-free conditions, while intact plasma fibronectin fails to stimulate **fibroblast** invasion. Pure PHSRN SEQ ID NO.:1 peptide has also been shown to stimulate keratinocyte invasion of serum-free SU-ECM. Since, during wound reepithelialization, keratinocytes **migrate** through the connective tissue of the provisional matrix to "wall off" portions of the wound, as well as through the. . .

AN 1999:163820 USPATFULL

PI US 6001965 19991214

TI Anticancer compounds and methods

human dermal fibroblasts to the wound matrix proteins, fibronectin, vitronectin, and fibrinogen)

IT Integrins

RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (.alpha.v.beta.1, role of .alpha.v and .beta.1 integrins in adhesion of human dermal fibroblasts to the wound matrix proteins, fibronectin, vitronectin, and fibrinogen)

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L11 ANSWER 32 OF 34 CAPLUS COPYRIGHT 2001 ACS

AB The role of fibrin in the generation of new blood vessels was examd. in this study. Using a **wound** chamber model, the authors investigated the sequential interactions between endothelial cells and the extracellular matrix during angiogenesis. Silicone tubes 5. . . chamber were removed at intervals for histol., immunohistochem. and electron microscopic studies. An initial phase of fluid accumulation in the **wound** chamber was followed by formation of a fibrin/fibronectin clot. **Migration** of endothelial cells, macrophages and **fibroblasts** into the clot occurred after the 1st week. The subsequent phase of fibrinolysis was accompanied by deposition of collagen and. . . indicate that fibrin is intimately involved in both hemostasis and angiogenesis; these are sequential steps in the initial phase of **wound** healing. Thus, fibrin/**fibrinogen** occupies a central position and provides a vital link in the initiation of the cascade event of **wound** healing.

AN 1991:556345 CAPLUS

DN 115:156345

TI Interactions between fibrin, collagen and endothelial cells in angiogensis